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USSR WORK ON INTERRELATION OF CHEMICAL STRUCTURE AND PHARMACOLOGICAL ACTIVITY OF CHOLINOLYTIC AGENTS

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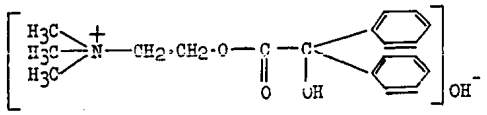
The chemical constitution of cholinolytic substances resembles that of cholinomimetic substances. As a rule, for every group of cholinomimetic substances there is a corresponding group of cholinolytic agents similar in constitution [1]. Accordingly, among cholinolytic agents one encounters substances which are similar in constitution to acetylcholine as well as substances which have little in common with acetylcholine in regard to constitution.

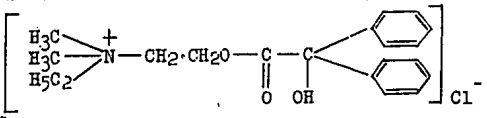
Cholinolytic substances can be derived from cholinomimetic substances by increasing the weight of their molecules in the alcohol moiety and especially in the acid moiety. Very active cholinolytic agents are obtained by introducing residues of aromatic acids, especially residues of aromatic hydroxyacids, into the molecule.

Thus, one may derive a cholinolytic drug from acetylcholine by replacing the hydrogen atoms in the latter's acid group with a hydroxyl and two phenyl radicals, i. e., by passing from the acetic acid ester to the benzilic acid ester (I).



(I)

The cholinolytic activity of I is increased still further by replacing one of the methyl radicals in the alcohol part with an ethyl radical:



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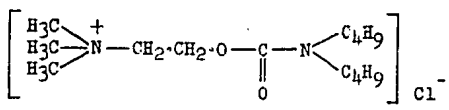
The benzilic acid ester of acetylcholine (I) as well as compound II, which is known as lachesine [lakhesin], are very similar in their constitution to acetylcholine. For this reason I and II in a manner similar to acetylcholine, affect both M-cholinoreactive systems and N-cholinoreactive systems, bringing about their blocking [2]. A cholinolytic agent of the same type was obtained by increasing the weight of the molecule of carbocholine:



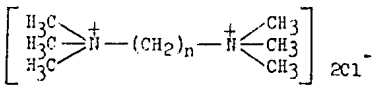
(III)

Compound III, which is known as dibutoline, can be described as a carbocholine in which both hydrogen atoms of the amino group in the acid moiety have been replaced by butyl groups. Dibutoline is likewise a poison which blocks both M-cholinoreactive systems and N-cholinoreactive systems [3].

Atropine (IV) is a drug which exhibits a selective action on M-cholinoreactive systems. This alkaloid is a tropic acid ester of tropine (V). Tropine itself produces a cholinomimetic action [4]. However, esterification of this aminoalcohol with an aromatic hydroxyacid (tropic acid) results in a substance possessing cholinolytic activity. Esterification of V with other aromatic hydroxyacids (e. g., mandelic acid) also leads to substances that have an activity of the atropine type (homatropine VI).

Quaternary bases of the alkyltrimethylammonium type, which can be regarded as having a constitution that corresponds to the "cationic head" of acetylcholine, produce a selective action on M-cholinoreactive systems. One of the bases of this type is tetramethylammonium. According to the general rule mentioned above, substances which exhibit a selective action toward N-cholinoreactive systems can be obtained by increasing the weight of tetramethylammonium. The bromide of tetraethylammonium (VII) is a substance of heavier molecular weight that has been derived from tetramethylammonium. This substance has been thoroughly investigated at our laboratory [not identified] by Z. I. Vedeneyeva [5]. This investigation showed that compound VII acts differently on the N-cholinoreactive systems of different tissues. One may conclude from this that such N-cholinoreactive systems are not completely identical from the biochemical standpoint. According to Vedeneyeva's results, VII exhibits the greatest affinity toward the N-cholinoreactive systems of parasympathetic ganglia.

An increase in the molecular weight of tetramethylammonium can also be achieved by connecting two tetramethylammonium groups with the aid of a hydrocarbon chain. This results in substance VIII.



(VIII)

Depending on the length of the hydrocarbon chain in VIII, substances which exhibit a different selective action with respect to various N-cholinoreactive systems can be obtained. With n=6, we obtain a drug the action of which consists predominantly in the blocking of ganglia; with n=10, we get a drug with a strong selective curare effect, i. e., the so-called "Deka" (decamethylene bis-trimethylammonium).

Unusually acting cholinolytic drugs can be obtained starting with diethylaminoethanol (IX) which, as is known, has cholinomimetic properties [4]. When IX is esterified with aromatic acids, substances exhibiting cholinolytic action are obtained. As an example of these cholinolytic substances, diphacyl

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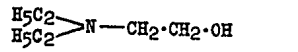
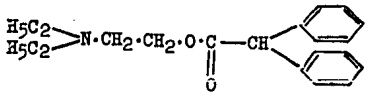
or spasmolytine (X) can be mentioned. Under the name of trasentine, X was put on the market abroad as a synthetic substitute for atropine, i. e., for a drug which has a selective action on M-cholinoreactive systems. However, it has been shown at our laboratory by T. N. Tomilina that diphacyl has a much more pronounced action on N-cholinoreactive systems than on M-cholinoreactive systems [6].



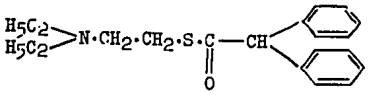
(IX)



(X)

The unusual characteristic of the activity of diphacyl consists in the so-called myotropic action of the diphacyl. This myotropic action may be regarded as an effect produced by the action of diphacyl on the biochemical processes which are directly responsible for the contractile activity of the smooth musculature. To characterize diphacyl completely, one must also mention the anesthetic effect it produces.

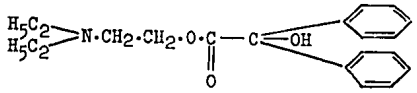
The sulfur-containing analog of diphacyl, thiphen (XI), closely resembles diphacyl in its pharmacological characteristics. Thiphen has been synthesized at VNIKhFI (All-Union Scientific Research Chemicopharmaceutical Institute imeni S. Ordzhonikidze) and has been investigated by M. D. Mashkovskiy and S. S. Liberman [7].



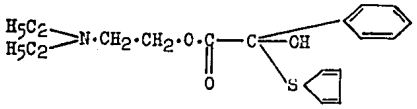
(XI)

As mentioned, a particularly high cholinolytic activity is achieved by esterifying alcohols with aromatic hydroxy acids. This rule was found to apply to the series of diethylaminoethanol derivatives [4]. When diethylaminoethanol is esterified with diphenylhydroxyacetic acid (benzilic acid), the compound designated in foreign literature as Win 5606 (XII) is obtained. Win 5606 proved to be much more effective than diphacyl.

The cholinolytic activity of XII can be enhanced still further by replacing one of its phenyl radicals in the acid moiety with a heterocyclic nucleus. An example of a compound of this type is Win 4779 (XIII).



(XII)



(XIII)

It should be noted that when the diethylaminoethanol derivatives indicated above are converted into the corresponding quaternary ammonium bases, i. e., their constitution brought nearer to acetylcholine, compounds with a stronger cholinolytic activity result. However, other pharmacological characteristics of the drugs disappear on conversion into quaternary salts. This

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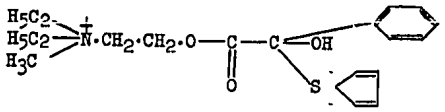
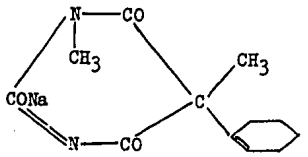
applies to the anesthetic and myotropic effects produced by them. For instance, lachesine (II), which may be regarded as a quaternary base analog of diphacyl (X), lacks these other pharmacological characteristics.

A very strong cholinolytic activity is shown by Win 5780 (XIV), which is a quaternary base analog of XII. Compound XIV has a cholinolytic activity 185 times stronger than that of diphacyl and 1½ times stronger than that of atropine. Although detailed information on the pharmacological action of XIV has not been published, one may conclude on the basis of the data cited above that XIV probably does not have any myotropic or anesthetic action.



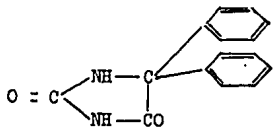
(XIV)

Among the cholinolytic substances mentioned above, there are, in addition to substances whose chemical constitution resembles acetylcholine, other substances which bear only a very remote chemical resemblance to acetylcholine. Furthermore, there are substances which have nothing in common with acetylcholine as far as their chemical constitution is concerned and which still exhibit a cholinolytic activity. For instance, N. S. Ratenberg's work established that a cholinolytic activity which affects N-cholinoreactive systems is exerted by hexenal (XV).



(XV)

I. G. Zavadskaya found that a cholinolytic activity affecting N-cholinoreactive systems is exhibited by diphenine (XVI), i. e., diphenylhydantoin [8].



(XVI)

The behavior of XV and XVI leads to the conclusion that the cholinolytic effect does not necessarily depend on the influence exerted by the active agent on the cholinoreactive system, i. e., on the identical link of tissue metabolism which is affected by acetylcholine. The assumption is plausible that blocking of biochemical processes in subsequent links of tissue metabolism will also bring about an effect which to all outer appearances will be similar to the cholinolytic effect.

Belen'kiy found that a cholinolytic effect at the chemical receptors of the carotid bulb can be obtained by means of sodium fluoride [9]. These data were confirmed by G. A. Mednikyan and S. I. Asratyan, who showed that cholinomimetic activity is exhibited by fluoride and other agents [10]. Earlier Kh. S. Koshtoyants had demonstrated that fluoride eliminates the vagus inhibition of the heart [11]. These facts support our assumption that

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cholinolytic effects probably depend not only on the action exerted by the drug on cholinoreactive systems but also on its action in influencing biochemical processes which are connected more directly with the functioning of the organ. The cholinolytic activity of fluoride cannot be explained as due to the blocking of cholinoreactive systems. It has been shown at our laboratory that while fluoride removes the effects of acetylcholine on the carotid bulb [9] and the upper cervical sympathetic ganglion [12], it does not remove these effects on the suprarenals [13] and even strengthens them in blood vessels [14].

As has been shown on the chemical receptors of the carotid bulb, cholinolytic effects are produced by other poisons besides fluoride (monoidoacetate, arsenite, and malonate) which disturb tissue metabolism [9]. The cholinolytic activity of magnesium ions is also apparently due to their action on links of tissue metabolism that are connected more directly with the functioning of organs than the cholinoreactive systems.

The concepts advanced above considerably widen our opportunities for modifying cholinergic processes with the aid of pharmacological agents. To carry out purposeful synthesis of new drugs affecting these processes, extensive research on the biochemical nature of these processes will be necessary. Biochemical research in this field will in turn require the application of pharmacological methods.

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